REMARKS

The Office Action dated April 13, 2010 has been carefully considered. Applicants submit that the present amendment is a proper amendment under 1.116 since it is for purposes merely of readying the claims for appeal. Claim 2 is amended to correct an improperly configured Markush claim, as pointed out by the Examiner in the April 13 action. Claim 1 is amended to further clarify that the detectable protecting groups of steps (a), (b) and (c) are the same. As no new matter is implicated, and since the scope of the claims remains the same, Applicants believe entry is warranted and respectfully request the same. There are no other substantive changes to the claims.

This Request for Reconsideration is being submitted with a Notice of Appeal.

Claims 1-3, 13, and 15-22 remain pending and subject to current examination.

Rejection under 35 USC §103

The rejection of **claims 1-3, 12, 13, and 15-22** under 35 USC §103(a) as being unpatentable over US Patent No. 6,238,862 to McGall et al (McGall), and Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997 (Wagner), in view of US Patent No. 5,151,507 to Hobbs et al (Hobbs) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and Agris (PGPUB 20020045167; 4/18/2002; cited previously) is maintained for reasons of record in addition to several additional reasons assertedly prompted by Applicants' last response. Summarily, the Examiner applies McGall for teaching quality control methods for measuring extent of deprotection in on-chip synthesis of oligonucleotides, applies Wagner for teaching a specific protecting chemistry for nucleobases, and applies Agris for addressing the problem of assessing deprotection of nucleobases (therefore ostensibly providing a motivation from the art to combine McGall and Wagner. Other references are cited for various dependent embodiments but do not address the primary combination vis a vis the independent claims.

This rejection is traversed, and reconsideration is respectfully requested.

Claim 1 is directed to a quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array. The method comprises (a) synthesizing a plurality of desired biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the

biopolymer array is complete, (b) taking one or more steps to cleave the detectable protecting groups, (c) determining a degree of deprotection by detecting any detectable protecting groups remaining on the array after cleavage, and (d) repeating steps (b) and (c) until detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip and wherein synthesized biopolymer species are not consumed or eliminated by practice of the method.

Applicants submit that although McGall teaches quality control methods relating to oligo array synthesis, McGall does not teach quality control methods relating to deprotection of the side amino groups, and McGall fails to teach or suggest quality control methods which do not consume or degrade the array being tested. McGall provides methods for assessing various aspects of on-chip light-directed oliognucleotide synthesis, including testing efficiency of nucleotide coupling, determining the extent to which a test condition causes deprotection of oliogonucleotides, methods for determining the extent of depurination of oligonucleotides, and detecting whether an array contains double-stranded nucleic acids. Careful inspection of McGall reveals that whereas the methods are conducted on-chip, the quality control aspect is with respect to the entire batch of chips manufactured, and not with respect to the individual chip tested, which is damaged and discarded as a result of the testing procedures disclosed (see, e.g. column 4, lines 27-33).

As noted by the Examiner, McGall does teach methods for determining degree of deprotection. Deprotection testing is disclosed specifically beginning at column 8, section IV "Deprotection Efficiency." The oligo-containing substrate (array or pseudo-array constructed for testing purposes) is divided into two areas which are subjected to different conditions. The protecting groups referred to in this section protect the active OH involved in the elongation reaction and are disclosed as detectable. Hence, impact of test conditions is easily determined by subjecting only one area of the array to the test conditions and determining the detection differential between the tested and non-tested areas.

Deprotection of side chain nucleobases consists of a brief mention made in passing in the section disclosing methods to determine coupling efficiency. At column 5, lines 8-9, McGall mentions as part of the general protocol that if side chain protective groups are present, they are removed. There is absolutely no teaching or motivation for coupling of **detectable** protecting groups on the side chain, nor is there any suggestion of a quality control method for measuring the extent or completeness of deprotection of the side chain nucleobases.

The Examiner cites to various specific teachings o McGall for purportedly disclosing or suggesting embodiments which falls within the scope of the instant claims (in view of Wagner's nucleobase protecting group). The Examiner points specifically to claims 4 and 12 for embodiments which "read on" the instant invention. According to McGall claim 1 from which claim 5 depends, synthesis occurs in high volumes and the "testing arrays [are] selected from among the high volume manufactured. Claim 4 broadly refers to the selected arrays being tested for amount of deprotection. No steps or other parameters of this testing are provided. The only guidance offerred by the spec suggests that the selected arrays are consumed or otherwise destroyed for testing purposes. According to the McGall method provided by claim 12, which relates to efficiency of monomer coupling, a test array is divided into two areas and comparison testing of inter alia, deprotection, is inspected. Applicants note first that the deprotection aspect of this method is with respect to the active sites involved in the elongagtion reaction. Moreover it is clear that these "test arrays" are not destined for the intended use of a chip, but are discarded after quality control testing. In every example, illustration and otherwise depicted or suggest embodiments, the oligo array is consumed or destroyed for purposes of testing and the results with respect to measured quality are meant to be extrapolated to the batch of arrays produced, rather than specific to the tested array. Applicants invention provides a quality control method applicable to each manufactured array. Due to the elegant simplicity of the instant methods, they may be conducted on a large-scale basis with respect to an entire batch, without consuming a single array. This concept is neither taught nor suggested in the art.

Applicants do not dispute that the basic methods for on-chip synthesis were well known, or that protection and deprotection of active groups have been exploited to direct synthesis for more than a decade. Nor do Applicants dispute that protection of nucleobases is known. Indeed, Applicants point this out along with examples of commonly employed protecting groups in the Background section of the instant specification. Applicants further note that the secondary references Agris expressly notes that extent of base deprotection upon deprotection after oligo synthesis is a known problem in the art (see, e.g. [0003]).

Applicants' invention addresses and solves the known problem of determining extent of deprotection of the nucleobase side chains (the active groups which do not participate in elongation of the oligo) of an oligo array after on-chip synthesis, while keeping the array intact and capable of functioning for its intended ultimate use. The instant inventive quality control methods hinge on the use of detectable nucleobase blocking groups which may be cleaved from the completed array without consumption or degradation of the array, and under conditions which do not otherwise destroy the integrity of the array.

McGall, the primary reference, discloses and provides methods of quality control of coupling efficiency as between monomeric building blocks, extent of deprotection under certain test conditions, and determination of percent double-strandedness. McGall is not concerned with quality control of the deprotection of the side chain nucleobases. McGall fails even to acknowledge the problem, commenting only briefly that side chain protection groups, if they exist, should be removed prior to conducting quality control for coupling efficiency. McGall fails to disclose protecting groups which would stay coupled to the active site until synthesis of an array is completed. Given that McGall teaches deprotecton of the OH protecting groups after each addition round of synthesis, it would be important to keep the side chain active sites protected until the end. However, McGall fails to teach or suggest any conditions or protecting groups which would accomplish this.

The Examiner applies Wagner for disclosure of methods of synthesis of various oligonucleotides using protected nucleotides and for teaching that a fluorescent label may be linked directly to the amino group of the nucleobases and for teaching detecting the protecting groups attached to the synthesized oligonucleotides and deprotection of the label attached nucleobase after the synthesis of the oligonucleotide, as well as for disclosure of certain elements recited in dependent embodiments. Wagner existed at the time of McGall. Applicants do not dispute that a nucleobase protecting group has been known since 1990. Applicants do not dispute that Wagner discloses a detectable nucleobase protecting group. However a detectable nucleobase protecting group has never been exploited for or applied to developing a quality control method for ensuring complete deprotection of nucleobases after synthesis of oligo arrays.

Critically, Applicants submit that the detectable nucleobase protecing group of Wagner, dnseoc, could not function in accordance with the instant methods, as it is touted specifically for a purpose that is expressly avoided by the instant invention. Wagner teaches that the dnseoc group is used for blocking the 5-OH funciton in oligo synthesis (see, e.g. page 200, middle of first paragraph; page 205, top of page) and that DBU treatment is used to remove all the protecting groups. Therefore, if the detectable protecting group of Wagner were imported into a quality control method of McGall with respect to deprotection of side chains, assuming arguendo that McGall even provides a foundation for this, the resulting method would not work because McGall teaches deprotection of the 5-OH at the end of each step in synthesis, which would result in deprotection of the side chains as well. The side-chains would have to be re-capped or protected at each monomeric addition step, whereas according to the instant methods deprotection of the side chains does not occur until the end of array synthesis.

Agris is applied for allegedly teaching the need for methods of monitoring the degree of deprotection of nucleobases upon completion of synthesis of oligonucleotides on arrays by detecting detectable protecting groups "on the array." Agris is essentially being applied to provide the motivation to combine the technologies of the other references to achieve a quality control method with respect to deprotection of the side chains. The Examiner argues that Agris teaches the need for "on-chip detection" so that simple and reliable techniques for determining the purity of the desired oligonucleotides on an array can be achieved.

Applicants admit that Agris expresses the problem known in the art and solved by the instant invention. Agris also provides a solution to the problem, but it is an entirely distinct solution, as noted by the Examiner. Agris uses antibodies to detect protected oligonucleotides in an immunoassay format, which would clearly reduce the yield of oligonucleotide since all those detected in the single detection step are eliminated from downstream uses. The Examiner argues, however, that Agris provides a motivation to combine McGall and Wagner by stating the need to determine the degree of deprotection of the nucleobase side chains and the desirability for a simple and reliable technique to control the quality of the synthesized microarray.

Applicants agree with the Agris thesis as stated by the Examiner and submit that they have provided such a simple and reliable technique, whereas the combined teachings of McGall and Wagner fail to provide a method that could operate to achieve deprotection of the side chains after completion of array synthesis. The method derived from the combination of McGall and Wagner clearly results in cleavage of all protected groups at the end of each unit addition step in the oligo synthesis.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). As set for the in detail above, the combination of McGall and Wagner, in view of Agris, fails to enable the instant invention. Without additional guidance, a person of ordinary skill in the art could not achieve a quality control method for deprotection of nucleobase protecting groups in accordance with the instant methods, which require deprotection of the amine-protected groups at the completion of array synthesis. Importing the detectable nucleobase protecting group of Wagner into the methods of McGall in view of a need for assessing extent of deprotection of nucleobase protected groups as disclosed by Agris, results in a method wherein all protecting groups are cleaved at the end of each unit addition round of oligo synthesis, whereas according to the instant methods, deprotection of the nucleobase occurs at the completion of synthesis of the oligo array.

Claim 1 and dependent claims 2-3, 13, and 15-22 are therefore nonobvious and patentable under 35 USC §103 over McGall and Wagner in view of Agris, further in view of Hobbs and Chen. Reconsideration is therefore respectfully requested.

Respectfully submitted,

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